ZYTIGA® (abiraterone acetate)
Adverse Event - Hematologic Effects

SUMMARY

- This response includes relevant data from the pivotal studies of ZYTIGA: COU-AA-301, COU-AA-302, and LATITUDE.
- **COU-AA-301** (NCT00638690) was a phase 3, randomized, double-blind, placebo-controlled, multinational study of ZYTIGA plus prednisone vs placebo plus prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) and disease progression after docetaxel-based chemotherapy (N=1195).[1]
  - The median follow-up was 12.8 months at the time of the interim analysis. The final analysis published by **Fizazi et al (2012)**[2] reported a median follow-up of 20.2 months. Grade 3 and 4 hematological adverse event (AE) rates for both ZYTIGA plus prednisone and placebo plus prednisone groups were consistent.[2]
- **COU-AA-302** (NCT00887198) was a phase 3, randomized, double-blind, placebo-controlled, multinational study of ZYTIGA plus prednisone vs placebo plus prednisone in asymptomatic or mildly symptomatic patients with chemotherapy-naïve mCRPC (N=1088). The median follow-up was 49.2 months. Hematologic events were not reported among the AEs in this study.[3,4]
- **LATITUDE** was a phase 3, randomized, double-blind, placebo-controlled study of ZYTIGA plus prednisone with androgen deprivation therapy (ADT) versus placebo with ADT in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (mCSPC). At the final analysis, at a median follow-up of 51.8 months, grade 3 and 4 hematological AEs were evaluated.[5,6]

CLINICAL DATA

COU-AA-301 Study

de Bono et al (2011)[1] evaluated the efficacy and safety of ZYTIGA plus prednisone compared to placebo plus prednisone in patients with mCRPC whose disease had progressed after docetaxel-based chemotherapy (N=1195).

Study Design/Methods

- Phase 3, randomized, double-blind, placebo-controlled, multinational study.
- Patients were randomized 2:1 to receive the following:
  - ZYTIGA 1,000 mg orally (PO) once daily and prednisone 5 mg PO twice daily (n=797) or placebo and prednisone 5 mg PO twice daily (n=398).
  - ADT, a gonadotropin-releasing hormone (GnRH) analog, or prior orchiectomy was required in both arms.[7]
- Study treatment continued until disease progression documented as based on prostate-specific antigen (PSA) concentration, radiographic imaging, and clinical findings.
- Selected inclusion criteria: patients who met hematologic and chemistry laboratory criteria, including serum albumin level ≥ 3.0 g/dL, hemoglobin ≥ 9.0 g/dL independent of transfusion, platelet count ≥ 100,000/µL, serum creatinine < 1.5 x ULN, and serum potassium ≥ 3.5 mmol/L were included in the study.[7]

Results

Key Safety Outcomes - Hematological Events

- The median follow-up was 12.8 months at the time of the interim analysis.[1]
- **Fizazi et al (2012)**[2] reported the final efficacy and safety analysis of COU-AA-301 study at a median follow up was 20.2 months.
- The rates of grade 3 and 4 AEs in both treatment groups revealed results consistent with those of the first interim analysis, as summarized in Table: Hematological AEs - Final Analysis.[2]

Hematological AEs - Final Analysis[2]

AE, n (%)	ZYTIGA+Prednisone (n=791)			Placebo+Prednisone (n=394)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Anemia	198 (25)	53 (7)	9 (1)	110 (28)	26 (7)	6 (2)
Thrombocytopenia	30 (4)	8 (1)	3 (<1)	15 (4)	1 (<1)	1 (<1)
Neutropenia	8 (1)	1 (<1)	0	2 (<1)	1 (<1)	0
Febrile neutropenia	3 (<1)	0	3 (<1)	0	0	0
Abbreviations: AE, adverse event.						

COU-AA-302 Study

Ryan et al (2013 and 2015)[3,4] evaluated the efficacy and safety of ZYTIGA plus prednisone compared to placebo plus prednisone in asymptomatic or mildly symptomatic patients with chemotherapy-naïve mCRPC (N=1088).

Study Design/Methods

- Phase 3, randomized, double-blind, placebo-controlled, multinational study.
- Patients were randomized to receive:
  - ZYTIGA 1000 mg PO once daily and prednisone 5 mg PO twice daily (n=546) or placebo and prednisone 5 mg PO twice daily (n=542).
  - ADT, GnRH analog, or prior orchiectomy was required in both arms.[8]
- Treatment continued until radiographic or clinical (cytotoxic chemotherapy, radiation or surgical treatment for cancer, pain requiring chronic opioids, or Eastern Cooperative Oncology Group performance status (ECOG PS) decline to 3 or more) disease progression, unacceptable toxicity, or withdrawal. Patients were allowed to continue blinded study medication after radiographic progressive disease in absence of unequivocal clinical progressive disease.[8]
- Select inclusion criteria: patients who met specific hematologic and chemistry laboratory parameters, including hemoglobin ≥ 10.0 g/dL independent of transfusion, platelet count ≥ 100,000/µL, and serum albumin ≥ 3.5 g/dL were included in the study[8]

Results

- **Ryan et al (2015)**[4] reported the final efficacy and safety analysis of the COU-AA-302 study at a median follow-up of 49.2 months.
- Hematologic events were not reported among the AEs in this study.

LATITUDE Study

Fizazi et al (2017 and 2019)[5,6] evaluated the efficacy and safety of ZYTIGA plus prednisone with ADT vs placebos with ADT for the treatment of newly diagnosed, high-risk mCSPC (N=1199).

Study Design/Methods

- Phase 3, randomized, double-blind, placebo-controlled, multinational, multicenter study.
- Patients were randomized 1:1 to receive either ZYTIGA 1,000 mg plus prednisone 5 mg PO daily with ADT (n=597) or placebo PO daily with ADT (n=602).
  - Patients were stratified by ECOG PS grade (0 or 1 vs 2) and by presence or absence of visceral disease.
  - Patients who had not had surgical castration received ongoing ADT to reach or maintain a serum testosterone level <50 ng/dL.
- Selected inclusion criteria: patients with adequate hematological functions including hemoglobin ≥ 9.0 g/dL (independent of transfusion), neutrophils ≥ 1.5 × 10^9/L, and platelets ≥ 100 × 10^9/L were included in the study.[9]

Results

Key Safety Outcomes - Hematological Events

- At the time of the final analysis, median follow-up was 51.8 months.[6]
- The rates of grade 3 and 4 hematological AEs in both treatment groups are summarized in Table: Hematological AEs in Any Group.

Hematological AEs in Any Group[6]

AE, n (%)	ZYTIGA+Prednisone+ADT (n=597)			Placebo+ADT (n=602)		
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Anemia	45 (8)	14 (2)	3 (1)	63 (10)	26 (4)	1 (<1)
Platelet count decreased	15 (3)	1 (<1)	1 (<1)	7 (1)	4 (1)	0
Thrombocytopenia	8 (1)	0	1 (<1)	8 (1)	3 (<1)	0
Neutropenia	5 (1)	3 (1)	1 (<1)	5 (1)	4 (1)	1 (<1)
Neutrophil count decreased	3 (1)	3 (1)	0	2 (<1)	1 (<1)	1 (<1)
Abbreviations: ADT, androgen deprivation therapy; AE, adverse event.						

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) was conducted on was conducted on 18 June 2025.

REFERENCES

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